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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/478,748	06/07/95	WALDMANN T	2026-4003US3

EXAMINER	
GAMBEL, P.	
ART UNIT	PAPER NUMBER
1806	9

DATE MAILED: 03/04/97

18M1/0304

NATIONAL INSTITUTES OF HEALTH
PATENT BRANCH
OFFICE OF TECHNOLOGY TRANSFER
BOX OTT
BETHESDA MD 20892

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 12/6/96

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-25 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-25 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. Applicant's amendment, filed 12/6/97 (Paper No. 8), is acknowledged. Claims 24-25 have been amended.

Claims 1-25 are pending and being acted upon presently.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 12/6/97 (Paper No. 8). The rejections of record can be found in the previous Office Action (Paper No. 7).

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

5. The rejection of claims 24-25 under 35 U.S.C. § 112, second paragraph, have been withdrawn in view of applicant's amendments, filed 12/6/97 (Paper No. 8).

6. The previous rejection of claim 24 under 35 U.S.C. § 102(b) as being anticipated by Kozak et al. (PNAS, 1986) has been withdrawn in view of applicant's amendments.

7. Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Ann. Oncol., 1994; 1449, #1) for the reasons of record (Paper No. 7).

Applicant's arguments, filed 12/6/97 (Paper No. 8), have been fully considered but are not found convincing.

Applicant argues that the reference does not teach or make any suggestion relating the effective dosage. However, the reference authored by applicant clearly teaches the use of same 5-15 mCi ^{90}Y-labeled anti-Tac antibody (page 16, column 1 paragraph 2). The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ^{90}Y-labeled anti-Tac antibody recited in the claims is a broad range and surely would be encompassed by the use of the same 5-15 mCi ^{90}Y-labeled anti-Tac antibody disclosed in the prior art.

In addition, Waldmann teaches the use of radiolabel and immunotoxin conjugated anti-Tac monoclonal antibodies, including those conjugated with ^{90}Y, ricin and pseudomonas in the treatment of the leukemias, lymphomas and autoimmune disease, the same teachings encompassed by the claimed methods and disclosed in the specification. The Office does not have the facilities for examining and comparing applicant's claimed range of 2-100 mg of anti-Tac antibody is any different from the amount of antibody disclosed in the prior art. However the reference clearly teaches the same amount of radioactive conjugate is provided with the same anti-Tac antibody for the same methods by the same person as that presently claimed. Applicant has not provided sufficient objective evidence to distinguish between the amount of antibody taught or known by virtue of the reference differs from that presently claimed. The claimed effective dosages are either taught by the references cited in this review article, or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. It is the burden of the applicant to show the unobvious difference between the claimed and disclosed pharmaceutical methods and compositions. Applicant's arguments have not been found persuasive in the absence of any objective evidence to the contrary.

Applicant essentially argues that the claims are drawn to the amount of antibody as well as the amount of radionuclide administered and one skilled in the art would not how much anti-Tac to conjugate in the amount of disclosed radionuclide to produce an effective treatment. The examiner maintains the amount of antibody is inherent in the amount of radiolabeled anti-Tac taught by the reference and was known or obvious at the time the invention was made including by applicant who authored the reference of record. Applicant's arguments have not been found persuasive in the absence of any objective evidence to the contrary.

8. Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Important Adv. Oncol., 1994) for the reasons of record (Paper No. 7).

Applicant's arguments, filed 12/6/97 (Paper No. 8), have been fully considered but are not found convincing.

Applicant argues that the reference does not teach or make any suggestion relating the effective dosage. Applicant argues that the reference describes the use of 5-15 μCi of ^{90}Y-labeled anti-Tac antibody (page 138). However, the reference authored by applicant appears to teach the use of same 5-15 mCi ^{90}Y-labeled anti-Tac antibody disclosed in Waldmann (Leukemia, 1993, cited as reference 22 in Waldmann, Important Adv. Oncol., 1994 and of record in the instant application, see 892 and the next section)(see page S154, column 1 or Leukemia, 1993) and which appears to be the same recitation of Waldmann (Ann. Oncol., 1994; page 16, column 1 paragraph 2) relied upon above in the previous section. Therefore,

the reference disclosure of 5-15 μCi of ^{90}Y-labeled anti-Tac antibody appears to be a mistake and should be 5-15 mCi ^{90}Y-labeled anti-Tac antibody, as the reference clearly indicates by its own citation as well as by applicant himself. The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ^{90}Y-labeled anti-Tac antibody recited in the claims is a broad range and surely would be encompassed by the use of the same 5-15 mCi ^{90}Y-labeled anti-Tac antibody disclosed in the prior art.

In addition, Waldmann teaches the use of radiolabel and immunotoxin conjugated anti-Tac monoclonal antibodies, including those conjugated with ^{90}Y, ricin and pseudomonas in the treatment of the leukemias, lymphomas and autoimmune disease, the same teachings encompassed by the claimed methods and disclosed in the specification. The Office does not have the facilities for examining and comparing applicant's claimed range of 2-100 mg of anti-Tac antibody is any different from the amount of antibody disclosed in the prior art. However the reference clearly teaches the same amount of radioactive conjugate is provided with the same anti-Tac antibody for the same methods by the same person as that presently claimed. Applicant has not provided sufficient objective evidence to distinguish between the amount of antibody taught or known by virtue of the reference differs from that presently claimed. The claimed effective dosages are either taught by the references cited in this review article, or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. It is the burden of the applicant to show the unobvious difference between the claimed and disclosed pharmaceutical methods and compositions.

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9. Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Leukemia, 1993) for the reasons of record (Paper No. 7).

Applicant's arguments, filed 12/6/97 (Paper No. 8), have been fully considered but are not found convincing.

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In addition, Waldmann teaches the use of radiolabel and immunotoxin conjugated anti-Tac monoclonal antibodies, including those conjugated with ^{90}Y, ricin and pseudomonas in the treatment of the leukemias, lymphomas and autoimmune disease, the same teachings encompassed by the claimed methods and disclosed in the specification. The Office does not have the facilities for examining and comparing applicant's claimed range of 2-100 mg of anti-Tac antibody is any different from the amount of antibody disclosed in the prior art. However the reference clearly teaches the same amount of radioactive conjugate is provided with the same anti-Tac antibody for the same methods by the same person as that presently claimed. Applicant has not provided sufficient objective evidence to distinguish between the amount of antibody taught or known by virtue of the reference differs from that presently claimed. The claimed effective dosages are either taught by the references cited in this review article, or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. It is the burden of the applicant to show the unobvious difference between the claimed and disclosed pharmaceutical methods and compositions.

Applicant essentially argues that the claims are drawn to the amount of antibody as well as the amount of radionuclide administered and one skilled in the art would not how much anti-Tac to conjugate in the amount of disclosed radionuclide to produce an effective treatment. The examiner maintains the amount of antibody is inherent in the amount of radiolabeled anti-Tac taught by the reference and was known or obvious at the time the invention was made including by applicant who authored the reference of record. Applicant's arguments have not been found persuasive in the absence of any objective evidence to the contrary.

10. Claims 1-14 and 16-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) for the reasons of record (Paper No. 7).

Applicant's arguments, filed 12/6/97 (Paper No. 8), have been fully considered but are not found convincing. Applicant argues the reference individually and not their combined teachings. Applicant is also reminded that it is obvious to optimize result effective variables known to impart desired therapeutic effect with the use of the same anti-Tac antibodies with the same conjugates as clearly taught by the references and that prior art which teaches a range within, overlapping, or touching the claimed range anticipates, if the prior art range discloses the claimed range with sufficient specificity.

As pointed out above in sections 7-9; the claimed effective dosages are either taught by the references cited in this review article, or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. For example, Waldmann et al. (Important Adv. Oncol., 1994) teaches that ^{90}Y-conjugated anti-Tac antibodies had improved efficacy compared top murine anti-Tac alone (page 16 , paragraph 2); therefore the amount of conjugated anti-Tac antibody was taught in the prior art and was compared with unconjugated anti-Tac antibodies to determine the efficacy of the conjugate in therapeutic efficacy. Applicant's reliance on the prior art teaching of 5-15 μCi clearly mischaracterizes the prior art teachings, as pointed out above in section 9. Again, applicant argues that deduction of the instant dosage ranges would require undue experimentation which appears to run contrary to various referenced teachings of the prior art which include review articles by applicant, which disclose the use and expected use of the same such conjugated anti-Tac antibodies for the same therapeutic modalities of the claimed invention. It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. Therefore, due to their common known purpose and the known toxicity of conjugated anti-Tac antibodies, it would have been obvious to use conjugated anti-Tac antibodies followed by unconjugated anti-Tac antibodies in therapeutic regimen to eliminate or reduce undesirable Tac-expressing cells. Therefore, applicant's arguments are not found persuasive and the rejection is maintained.

11. Claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) as applied to claims 1-14 and 16-25 above and in further view of Parenteau et al. (Transplantation et al.) for the reasons of record (Paper No. 7).

Applicant's arguments, filed 12/6/97 (Paper No. 8), have been fully considered but are not found convincing.

Applicant argues that none of the references alone or in combination would lead the skilled artisan to a reasonable expectation of success in selecting the correct amount of anti-Tac conjugated to the correct amount of ^{90}Y without undue experimentation. Again as pointed out above in section 10, applicant's arguments run contrary to the combined references of record including applicant's own work which includes Parenteau et al. as well Parententeau et al. clearly discusses the use of such combinations in the context of human therapy with an expectation of success. Therefore, applicant's arguments are not found persuasive and the rejection is maintained.

12. As pointed out in the previous Office Action (Paper No. 7); in the event that applicant intends that the claimed pharmaceutical compositions (claims 24-25) are drawn to anti-Tac antibody pharmaceutical compositions which find written support in parent applications, the following rejection of record in copending USSN 07/879,056 was set forth. Applicant's amendment, filed 12/6/96 (Paper No. 8) does not make it clear what is the priority date of amended claims 25-26.

Claims 24-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Kozak et al. (PNAS, 1986) or Diamantstein et al. (Immunol. Rev., 1986) in view of Order et al. (Int. J. Radiat. Oncol. Biol. Phys., 1986) or Wessels et al. (Med. Phys., 1984) for the reasons of record (Paper No. 7).

Applicant's arguments, filed 12/6/97 (Paper No. 8), have been fully considered but are not found convincing.

Applicant argues the references individually and not their combination. Applicant argues that Diamanstein is not directly pertinent in evaluating the prior art concerning radioimmunosuppressive therapy methods and that there is no disclosure of the in vivo use of anti-Tac antibodies conjugated with a β-emitting isotope. Diamanstein and Kozak do not teach the use of an α-emitting isotope at the exclusion of a β-emitting isotope. Wessels and Order provide evidence that a β-emitting isotope is an effective radioisotope in eliminating unwanted cells and therefore would have been applicable to the teachings of Diamanstein and Kozak. It is noted that page 5, paragraph 1 of applicant's disclosure makes no distinction between α-

emitting isotope such as ^{212}Bismuth with a β-emitting isotope such as ^{90}Yttrium. Applicant is reminded that the instant claims are drawn to pharmaceutical compositions and not methods. The combined references of record clearly provide motivation to conjugated anti-Tac antibodies with various conjugates including a β-emitting isotope such as ^{90}Yttrium as a radio-immunotherapeutic reagent for the reasons of record to eliminate unwanted Tac positive cells observed in a number of T-cell mediated disorders in humans. Therefore, applicant's arguments are not found persuasive and the rejection is maintained.

13. Claims 1-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (1-5, 13, 22 and 28) of copending application Serial No. 07/879,056 in view of Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) for the reasons of record (Paper No. 7).

Claims 1-25 are directed to an invention not patentably distinct from claims (1-5, 13, 22 and 28) of commonly assigned USSN 07/879,056 in view of Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) for the reasons of record (Paper No. 7).

Should the claims of copending USSN 07/879,056 be allowed, a terminal disclaimed will be filed at that time. See applicant's amendment, filed 12/6/97 (Paper No. 8),

14. No claim is allowed.

15. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

16. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $375 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

17. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
February 24, 1997